Pathogenesis of ataxia-telangiectasia: the next generation of ATM functions.

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Authors: Mark Ambrose, Richard A Gatti

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Public Summary:
Since the identification of gene(ATM)responsible for ataxia- telangiectasia (A-T) autosomal recessive disease, most studies have focused on its nuclear function in the early recognition and response to double-stranded DNA breaks. ATM also plays many important cytoplasmic roles. Appreciating these roles helps to provide new insights into the diverse clinical phenotypes exhibited by A-T patients -- children and adults alike -- which include neurodegeneration, high cancer risk, adverse reactions to radiation and chemotherapy, pulmonary failure, immunodeficiency, glucose transporter aberrations, insulin-resistant diabetogenic responses, and distinct chromosomal and chromatin changes. Most exciting recently is the ATM-dependent pathology encountered in mitochondria, leading to inefficient respiration and energy metabolism and the excessive generation of free radicals that themselves create life-threatening DNA lesions that must be repaired within minutes to minimize individual cell losses.

Scientific Abstract:
Twenty-five years ago, the gene responsible for the autosomal recessive disease ataxia- telangiectasia (A-T) was localized to 11q22.3-23.1. It was eventually cloned in 1995. Many independent laboratories have since demonstrated that in replicating cells ATM is predominantly a nuclear protein that is involved in the early recognition and response to double-stranded DNA breaks. ATM is a high molecular weight PI3K-family kinase. ATM also plays many important cytoplasmic roles where it phosphorylates hundreds of protein substrates that activate and coordinate cell signaling pathways involved in cell cycle checkpoints, nuclear localization, gene transcription and expression, the response to oxidative stress, apoptosis, nonsense mediated decay, and others. Appreciating these roles helps to provide new insights into the diverse clinical phenotypes exhibited by A-T patients -- children and adults alike -- which include neurodegeneration, high cancer risk, adverse reactions to radiation and chemotherapy, pulmonary failure, immunodeficiency, glucose transporter aberrations, insulin-resistant diabetogenic responses, and distinct chromosomal and chromatin changes. Most exciting recently is the ATM-dependent pathology encountered in mitochondria, leading to inefficient respiration and energy metabolism and the excessive generation of free radicals that themselves create life-threatening DNA lesions that must be repaired within minutes to minimize individual cell losses.